REMARKS

Claims 1, 2, 5, 6, 8 and 9 are pending.

Claims 11-24 stand withdrawn.

Claims 1, 2, 5, 6, 8 and 9 stand non-finally rejected.

No new claims have been added.

Claims 3, 4, 7 and 10 have been canceled without prejudice to filing a continuing application claiming any canceled subject matter.

Claims 1, 2, 5, 6, 8 and 9 have been amended without prejudice to filing a continuing application claiming any deleted subject matter. The claims have been amended to more particularly point out and distinctly claim the subject matter Applicants regard as their invention. Support for the amendments is found in the application as originally filed. No new matter has been added.

As set forth in the Office Action at attachment 1, Applicants acknowledge the Notice of References Cited.

As set forth in the Office Action at p. 2, Applicants acknowledge withdrawal of the prior rejection under 35 U.S.C. § 112, 2nd Paragraph, as well as any prior rejections not reiterated in the present Office Action.

Applicants respectfully traverse the rejections of record and request reconsideration and withdrawal of the outstanding rejections and early allowance of the application.

With respect to the "Response to Arguments" section of the Office Action at pp. 2-4, Applicants acknowledge the assertion that none of the prior art of record discloses "the anti-androgenic activity of the claimed compounds."

The Nonenablement Rejection

At pp. 4-13 of the Office Action, 1, 5, 8 and 9 are rejected under 35 U.S.C. § 112, First Paragraph, as being nonenabled. Applicants respectfully traverse the rejection.

Regarding factor 1, Applicants acknowledge that "the relative skill of those in the art is high, generally that of an M.D. or Ph.D." and such skill level is "outweighed, however, by the unpredictable nature of the art." (P. 6)(underline added). Applicants further acknowledge

that the unpredictability of the relevant art is supported in the references cited in the Office Action. (See pp. 7-8).

Regarding factor 2, Applicants have amended claims 1, 5 and 8 to cover PMCol, C_{2-3} homologs of PMCol, and pharmaceutically acceptable salts thereof. Applicants submit that it has been well-established that (absent evidence to the contrary) biological activity of such proximate alkyl homologs and salts is predictable given the proven biological activity of PMCol. (See also, Office Action at p. 18). Claim 9 is directed to PMCol *per se* and pharmaceutically acceptable salts thereof. Claims 1, 5, 8 and 9 have also been amended recite "androgen-dependent prostate cancer."

Regarding factor 3, Applicants respectfully submit that one of ordinary skill in the art (e.g., a Ph.D. chemist) would know how to make and use the instantly claimed PMCol, C_{1-3} simple alkyl homologs thereof, and pharmaceutically acceptable salts thereof. Applicants further respectfully submit that the instant specification (see, e.g., Figs. 2, 3, 4, 5, 6, 7 and 8) is replete with actual *in vitro* and animal dosing data that is relevant and probative of PMCol being biologically active respecting androgen-dependent prostate cancer tumor cells.

Applicants further submit that the instant specification provides sufficient data and information to enable one of ordinary skill in the art (i.e., a medicinal chemist having a Ph.D. and a few years of experience) using routine experimentation to formulate useful doses and dosage forms containing the PMCol (or C_{2-3} homologs or pharmaceutically acceptable salts thereof) as the active pharmaceutical ingredient. Applicants still further submit that it has been accepted in the art that *in vitro* tests conducted using the LNCaP and LAPC4 prostate carcinoma cell lines are sufficiently and reasonably predictive of biological activity in humans. In this case, human clinical data is simply not necessary to *prima facie* establish biological activity of PMCol, C_{2-3} homologs thereof and salts thereof respecting androgen-dependent prostate cancer.

Regarding factor 4, the instant claims are directed at "androgen-dependent prostate cancer" as well as PMCol, C_{2-3} homologs thereof, and salts thereof. Applicants respectfully submit that claims 1, 5, 8 and 9 are commensurate in scope with the data and information contained in the instant specification.

The Obviousness Rejection

At pp. 13-18 of the Office Action, claims 1, 2, 5 and 6 are rejected under 35 U.S.C. § 103(a) as being obvious over Gunawardena et al. ("Gunawardena") in view of Sheu et al. ("Sheu"). Applicants respectfully traverse the rejection.

The Claimed Invention

Method of use claims 2 and 6 have been amended to cover using PMCol and pharmaceutically acceptable salts "for inhibiting the growth of androgen-dependent prostate cancer tumor cells in a human" (claim 2) and for "delaying the progression of androgen-dependent prostate cancer in a human" (claim 6). Method of use claims 1 and 5 have been amended to cover using a genus of compounds (whereby the genus excludes α-tocopherol) for "inhibiting the growth of androgen-dependent prostate cancer tumor cells in a human" (claim 1) and for "delaying the progression of androgen-dependent prostate cancer in a human" (claim 5). The instantly claimed invention demonstrates that even when the hydrophobic ring of vitamin E is cleaved, the resulting PMCol still penetrates cells imparting efficacy and activity, which is strong evidence of nonobviousness.

The Gunawardena Reference

Gunawardena discloses testing known antioxidants including vitamin E, PDTC and DETC for use in treating prostate cancer cell growth. PMC is not disclosed. Moreover, PDTC and DETC are structurally dissimilar to PMC.

Gunawardena teaches that α-tocopherol "was less potent in modifying prostate cancer cell growth than the antioxidants PDTC and DETC." (Pp. 292, first col.). Gunawardena also suggests that α-tocopherol "did not cause growth inhibition in the androgen-unresponsive DU-145 cell line, whereas it did significantly affect growth of the androgen-responsive cell lines." (Id.)

Applicant submit that growth inhibition of androgen dependent cell line does not logically or predictably mean that the inhibitory compound is an anti-androgenic. There are many cytotoxic compounds such as doxorubicin, doecetaxol, etc. that inhibit growth of androgen dependent cells without showing anti-androgenic activity, and vitamin E has very poor anti-androgenic activity apart from growth inhibition of androgen-dependent cells.

Thus, Gunawardena teaches away from the instantly claimed invention by suggesting that α-tocopherol lacks anti-androgen activity in comparison to other known antioxidants, which is strong secondary evidence of nonobviousness.

The Sheu Reference

Sheu teaches that 2,2,5,7,8-pentamethyl-6-hydroxychromane (i.e., PMCol which is the compound shown in instant claims 2, 6 and 9) is a potent antioxidant useful for inhibiting human platelet aggregation. Sheu fails, however, to disclose using PMCol to inhibit growth of androgen-dependent prostate cancer tumor cells or to delay progression of androgen-dependent prostate cancer. Sheu essentially teaches that PMCol is "6-times more potent than α-tocopherol" on platelet aggregation and antioxidant activity. (Summary at pp. 197).

Sheu is silent with respect to other therapeutic indications, such as cancer, prostate cancer, or any sort of androgenic activity. Sheu also fails to suggest that PMC penetrates cells and causes activity.

Sheu et al teaches that certain anti-oxidants, such as PMC, inhibits platelet aggregation by scavenging free radicals, and that PMC may be somewhat more potent than vitamin E at such. However, Applicants respectfully submit that the data in Sheu fails to even remotely suggest that PMC would have been anti-androgenic or anti-cancerous. Nor does the Sheu data suggest any relationship between PMC and vitamin E for treating any form of cancer let alone androgen-dependent prostate cancer.

Applicants further submit that one of ordinary skill could not reasonably predict that a compound demonstrating anti-platelet aggregating activity would also have anti-cancer activity. Sheu's mere suggestion that PMC may have antioxidant activity is not reasonably predictive that PMC would demonstrate anti-androgen or anti-cancer activity. For example, as set forth in Barrett S., 1999, *High Doses of Vitamin C Are Not Effective as a Cancer Treatment* (http://www.quackwatch.com/01QuackeryRelatedTopics/Cancer/c.html), ascorbic acid (vitamin C) is a known antioxidant, but is not useful for treating cancer.

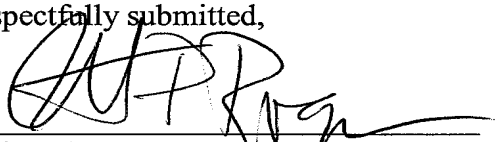
In addition, the instant specification provides further secondary evidence of nonobviousness. Fig. 2 compares the binding of PMCol, PMC and bicalutamide in human prostate carcinoma cells. As shown in the graphs and as compared to PMC and bicalutamide,

PMCol demonstrated unexpectedly and synergistically superior binding activity, which is strong secondary evidence of nonobviousness.

Thus, Gunawardena and Sheu (alone or in combination) fail to establish a *prima facie* case of obviousness over claims 1, 2 5 and 6, particularly in view of the unpredictability of the art. Moreover, the claimed invention is patentably nonobvious in view of the highly probative evidence secondary considerations of nonobviousness set forth above. Reconsideration and withdrawal of the rejection is respectfully requested.

The Commissioner is authorized to charge any fees under 37 C.F.R. § 1.17 that may be due on this application to Deposit Account 17-0055. The Commissioner is also authorized to treat this amendment and any future reply in this matter requiring a petition for an extension of time as incorporating a petition for extension of time for the appropriate length of time as provided by 37 C.F.R. § 136(a)(3).

Respectfully submitted,



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